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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,382	03/14/2001	Benjamin Eithan Reubinoff	14418	1139

7590 10/05/2007
SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, NY 11530

EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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10/05/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/808,382

Applicant(s)

REUBINOFF ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 7/13/07.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 39,44,45,51,56,57,60,61,67,86,94,101 and 105-113 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 39,44,45,51,56,57,60,61,67,86,94,101 and 105-113 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/13/07 has been entered.

Applicants' Remarks, filed 7/13/07, have been considered and entered. Claims 1-38, 40-43, 46-50, 52-55, 58, 59, 62-66, 68-85, 87-93, 95-100, 102-104 are cancelled; claims 39, 51, 56, 60, 61, 67, 94, 101 are amended; claims 105-113 are newly added; claims 39, 44, 45, 51, 56, 57, 60, 61, 67, 86, 94, 101, 105-113 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39, 44, 45, 60, 61, 67, 94, 101, 105, 106, 108, 110, 111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims require culturing pluripotent hES cells under adherent conditions for 2-3 weeks to generate differentiating cells. The specification only teaches culturing hES cells for 2-3 weeks on mouse embryonic fibroblast feeder cells for 2-3 weeks to generate differentiating cells. However, the

genus of "2-3 weeks of culturing hES cells under adherent conditions", which, when constructed and used as claimed, to produce differentiating cells, lacks a written description, and as such, there is no indication that Applicants had possession of the claimed invention.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the claimed invention in a detailed drawing, or by describing the invention with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole), such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the breath of the genus of "adherent conditions" lacks a written description.

The skilled artisan cannot envision the various adherent conditions under which to culture hES cells, to produce differentiating cells, that are encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. For example, "adherent conditions" can encompass merely culturing cells on plastic, or any variety of substrates. The instantly filed specification does not provide a specific definition for the term "adherent conditions," with regard to the production of differentiating cells after culture for 2-3 weeks. Therefore, only culturing hES cells on mouse embryonic fibroblast feeders are described by the as-filed disclosure.

Additionally, the claims 105-106 recite selecting cells, "destined to give rise to neural progenitor cells based on cell morphology;" and specifically, by "a density or a size". These limitations fails to be fully described by the as-filed disclosure. The specification teaches that the cells can be separated by density or morphology (see pages 38-39, bridging ¶). However, the specification does not provide any

description as to what density or size a cell that is "destined to give rise to a neural progenitor cell" would have. One of skill in the art could not envision the various densities or sizes these cells would have, and further, lacking any specific characteristics, these terms fail to have description, in the invention as a whole.

Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 51, 86, 107, 108 are rejected under 35 U.S.C. 102(b) as being anticipated by Brustle (Canadian Patent, CA 2315538, published 7/1/99).

The claims are directed methods of inducing differentiation of neural progenitors into neurons by obtaining neural progenitor cells derived from hES cells *in vitro*, wherein the neural progenitor cells express polysialated N-CAM, nestin, vimentin and the transcription factor Pax-6; culturing the neural progenitor cells on

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an adhesive substrate in the presence of a serum free media and growth factors; and inducing the neural progenitor cells to differentiate into neurons by withdrawal of the growth factors; and determining an expression of a neuronal cell marker of a neuronal cell marker (claim 51), wherein the cells are mature neurons (claim 86); wherein the neuronal cell marker is selected from the group consisting of 200 kDa neurofilament protein, 160 kDa neurofilament protein, MAP2a+b, glutamate, synaptophysin, glutamic acid decarboxylase and β -tubulin. Other embodiments are directed to methods of producing human neural progenitor cells from hES cells *in vitro*, the method comprising culturing undifferentiated pluripotent hES cells in serum free medium supplemented with growth factors which include epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), thereby obtaining neural progenitor cells, wherein said neural progenitor cells are capable of further differentiation into neurons, into oligodendrocytes, and into astrocytes, and wherein said neural progenitor cells express polysialated N-CAM, nestin, vimentin and the transcription factor Pax-6 (claim 108).

Brustle teach methods of producing neural precursor cells from human ES cells. See Abstract and p. 8, line 14. They teach the proliferation of ES cells, culturing of the ES cells to a neural precursor stage, proliferation of the neural precursor cell in growth factor-containing serum-free medium, and isolation of the purified precursor cell (see p. 8, lines 23-27), they teach that the serum-free medium contains bFGF and EGF (p. 8, line 35). They teach using these methods with mouse ES cells, they were able to produce neurons (see page 11, line 15, page 12, line 28). They teach culturing undifferentiated neural precursor cells in culture dishes coated with polyornithin and fibronectin to produce neurons, See page 16, lines 23-30). They teach the staining of the cells against antibodies to neuronal markers in order to determine the presence of neurons (see p. 16, lines 30-34).

Note that although Brustle do not explicitly teach all of the specific markers recited in the claims, they show the production of the cells required by the claims,

and thus, these cells would necessarily express these markers. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993), which teaches that a reference teaching a claimed process, wherein one of the claimed properties of a product used in the prior art process is inherent but undisclosed by the reference, may be properly applied as art against the claimed process. Additionally, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, because Brustle teach the same method steps, with the exact same reagents, and cells, they anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following rejections have been withdrawn:

1. The prior rejection of claims 39, 44-46, 60, 63, 64, 67, 100-104 as being unpatentable over Thomson *et al.* in view of Brustle is withdrawn in view of Applicants' amendment to the claim 39, which now requires culturing the undifferentiated hES cells for 2-3 weeks under adherent conditions.
2. The prior rejection of claims 68 and 94 under 35 U.S.C. 103(a) as being unpatentable over Thomson and Brustle in further in view of Ben-Hur is withdrawn. Claim 68 is cancelled; claim 94 depends from claim 39, which requires the limitation of culturing the undifferentiated hES cells for 2-3 weeks under adherent conditions.
3. The prior rejection of claims 61, 63 under 35 U.S.C. 103(a) as being unpatentable over Thomson in view of Brustle in view of Stemple, and further in view of Ben-Hur is withdrawn. Claim 63 is cancelled; claim 61 depends from claim 39, which requires the limitation of culturing the undifferentiated hES cells for 2-3 weeks under adherent conditions.

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 51, 86, 107, 108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* in view of Brustle. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 6/1/06 and 11/21/05.

Applicants' Arguments. Applicants' argue that Brustle do not teach culturing hES cells under adherent conditions for 2-3 weeks (see p. 10). Additionally, Applicants argue that although Brustle may inherently comprise some neuronal cells, Applicants' submit that the fact a certain characteristic may be present in the prior art is not sufficient to establish the inherency or result of the characteristic. Additionally, Applicants argue that the conditions and techniques of the instant invention do not allow for the generation of embryoid bodies, wherein the culturing techniques of Brustle produce embryoid bodies. Therefore, Applicants argue that the claims are neither taught or suggested by the combination of art. See page 10.

Response To Arguments. These arguments have been found persuasive with regard to claims that recite that the cells are cultured for 2-3 weeks under adherent conditions (claim 39 and dependent claims thereof), and claims that recite that the culturing does not result in embryoid bodies (claim 110). However, none of claims 51, 86, 107, 108 require this culturing step. Thus, the prior rejection of record renders these claims obvious. Furthermore, it is maintained that one of skill in the art, at the time of filing, would have recognized differences between hES cells and mES cells, particularly with regard to culturing the cells in presence of LIF. However, one of skill in the art would have also recognized that hES cells had the

capacity to differentiate into cell types from all three embryonic germ layers, including cells of neuronal lineage (as taught by Thomson). One of skill in the art would recognize that protocol existed to direct differentiation of mouse ES cells to a particular cell type (such as neuronal cells) (as taught by Brustle). The claims do not require a particular yield or amount of cells to be produced, thus, one of skill would have a reasonable expectation, given the combined teachings, to produce at least one NPC that would be capable of differentiation to cells of neurons, oligodendrocytes, and astrocytes. One of skill in the art would be motivated to use this protocol on human ES cells, with a reasonable expectation of success. Accordingly, the prior rejection is maintained.

Claims 56, 57, 112, 113 stand rejected under 35 U.S.C. 103(a) as being unpatentable Thomson *et al.* in view of Brustle *et al.* as applied to claims 51, 56, 57, 86, 107, 108, 112, 113 above, and further in view of Stemple *et al.* This rejection is maintained for reasons of record, advanced in the prior Office actions.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. It is maintained that, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in serum free media in the presence of FGF2 and PDGF-AA on polyornithine to form neural precursors, as taught by Brustle, but growing the precursors in a media comprising retinoic acid and growth on poly-D-lysine and laminin coated plates to induce neuronal growth, as taught by Stemple, for drug discovery and/or transplantation therapies. The methods will necessarily result in neural progenitor cells that express the particular markers claimed, because the claims require the same growth factors and medium. The cited prior art provides sufficient suggestion, teaching and motivation to arrive at the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

New Rejection

Claims 56, 57, 112, 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brustle (Canadian Patent, CA 2315538, published 7/1/99, above) in view of Stemple *et al.* (cited previously).

Brustle teach methods of producing neural precursor cells from human ES cells. See Abstract and p. 8, line 14.. They teach the proliferation of ES cells, culturing of the ES cells to a neural precursor stage, proliferation of the neural precursor cell in growth factor-containing serum-free medium, and isolation of the purified precursor cell (see p. 8, lines 23-27), they teach that the serum-free medium contains bFGF and EGF (p. 8, line 35). They teach using these methods with mouse ES cells, they were able to produce neurons (see page 11, line 15, page 12, line 28). They teach culturing undifferentiated neural precursor cells in culture dishes coated with polyornithin and fibronectin to produce neurons, See page 16, lines 23-30). They teach the staining of the cells against antibodies to neuronal markers in order to determine the presence of neurons (see p. 16, lines 30-34).

Stemple also teaches the growth of the neural stem cells in the presence of retinoic acid (page 983, col. 1, parag. 3, line 11-12). Laminin was known at the time of the instant invention to be an adhesive substrate for neural cell growth and differentiation.

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells as taught by Thomson in DMEM/F12 media in the presence of FGF2 and EGF on polyornithine to form neural precursors as taught by Brustle by growing the precursors in media comprising retinoic acid and by growth on poly-D-lysine and laminin coated plates to induce neuronal growth as taught by Stemple for drug discovery and/or transplantation therapies.

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The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
Art Unit 1632